Drug product:	N/A	**SYNOPSIS**	
Drug substance(s):	AZD8309		
Study code:	D1511C00002		
Date:	15 November 2006		

A Randomised, Double-Blind, Placebo-Controlled, Two-Way Crossover Study in Healthy Volunteers to Investigate the Effect of Oral Dosing with AZD8309 on Airway Inflammation as Assessed in Induced Sputum after Challenge with Inhaled Lipopolysaccharide (LPS)

Principal investigator

[redacted]

Study centre

[redacted]

Publications

None at the time of this report.

Study dates		**Phase of development**
First subject enrolled	06 September 2005	Therapeutic exploratory (II)
Last subject completed	16 February 2006	

Objectives

The primary objective of this study was to investigate the effect of AZD8309 compared to placebo treatment on neutrophil numbers in induced sputum after administration of inhaled LPS.

Secondary objectives of the study were to:

- Investigate the effect of AZD8309 compared to placebo treatment on soluble mediators in induced sputum after administration of inhaled LPS.
- Investigate the effect of AZD8309 compared to placebo treatment on cells and inflammatory mediators in blood after administration of inhaled LPS.

- Generate additional safety and tolerability data for AZD8309 dosed at 300 mg twice daily (bid).
- Collect blood samples that can be used for potential genetic analysis.
- Preliminary investigate the relationship between exposure and a change in neutrophils in sputum, if appropriate.

Study design

Randomised, double-blind, placebo-controlled, 2-way crossover study.

Target subject population and sample size

Healthy male or post-menopausal/surgically sterile females aged 18 to 50 years inclusive. Twenty subjects were to be randomised into the study to ensure a minimum of 16 subjects completed the study.

Investigational product, comparator: dosage, mode of administration and batch numbers

AZD8309 300 mg solution administered orally twice a day (bid). Batch numbers: [redacted]

Placebo to AZD8309 solution administered orally bid. Batch numbers: [redacted], [redacted]

Duration of treatment

Each subject received AZD8309 or placebo bid for 3 days.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: Neutrophil numbers in induced sputum
- Secondary variables:
  - Soluble mediators (IL-8, GROα, LTB_4, myeloperoxidase (MPO), neutrophil elastase (NE) in supernatant from induced sputum.
  - Blood analytes: Cell differential counts (neutrophils, monocytes, lymphocytes, basophils, eosinophils), soluble mediators (TNFα, high sensitivity CRP, IL-6, IL-8 & GROα) and serum amyloid A in blood.
  - AZD8309 plasma concentrations, and derived variables (C_{min}, C_{max}, t_{max}. $AUC_{(0\text{-}12h)}$, $t_{1/2}$)

Safety

Adverse Events, vital signs, 12-lead ECG, laboratory assessments (haematology, clinical chemistry and urinalysis), FEV_1, body temperature, and physical examination.

Statistical methods

Descriptive statistics were used for all parameters in the study.

Subject population

A total of 40 subjects were enrolled at 1 centre. Of these, 20 were randomised to treatment sequence at Visit 2, and 16 completed the study. Four subjects were withdrawn from the study after taking at least one dose of study drug; one of these discontinued due to an AE. All subjects were included in the analysis, both for efficacy and safety.

All subjects allocated to treatment (20 [100%]) were males. Their average age was 26 years (range: 19-44). Sixteen were Caucasian, 3 were Black and 1 was 'Other' race (Asian).

Efficacy and pharmacokinetic results

Statistically significantly fewer neutrophils were found in induced sputum (primary variable) in the AZD8309 group than in the placebo group (79% lower; p=0.027). The total leucocyte population in sputum was also lower in the AZD8309 group (77% lower; p<0.001), mainly as a result of the decrease in neutrophils, but a decrease in macrophages in the AZD8309 group also contributed to this effect.

Lower levels of all soluble mediators measured in induced sputum were observed in the AZD8309 group than in the placebo group (neutrophil elastase [35% lower; p=0.012)], IL-8 [52% lower; p=0.1], GROα [25% lower; p=0.044] and LTB_4 [39% lower; p=0.075]. MPO data were not available at the time of writing this report.

In blood, within 7 hours after the first dose, the total leucocyte count was 19% lower in the AZD8309 group than the placebo group, mostly because of a reduction in circulating neutrophils, which were on average 29% lower on AZD8309 than placebo. After LPS challenge, there were no differences between treatment groups in mean levels of neutrophils. At one hour post-dose on Day 3, just before LPS challenge, a total of 3 (20%) subjects had neutrophil counts below 1×10^9/L after treatment with AZD8309; there were none after placebo.

There were no apparent differences between the treatment groups in blood hsCRP and IL-6 levels. The majority of values obtained for TNFα (both groups) and IL-8 (placebo group) were below the LOQ. It was notable, however, that at 7 h all subjects in the AZD8309 group had circulating levels of IL-8 above the LOQ. Serum GROα and serum amyloid A data were not available at the time of writing this report.

Following administration of AZD8309 300 mg, all subjects achieved C_{min} levels >0.5 μM ($3 \times pA_2$) over the 12-hour dosing interval.

Safety results

There were no deaths, SAEs or other significant AEs during the study. One subject receiving placebo discontinued the study due to AEs. The most frequently reported AEs were pyrexia and headache and in general AEs were balanced across the treatments. A total of 44 AEs were of mild intensity and 3 (all on placebo) were of moderate intensity. Twelve AEs (8 on AZD8309; 4 on placebo) were judged by the investigator to be caused by the study drug.

Table S1 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events

	AZD8309 300 mg **n=18**	**Placebo** **n=19**
Number of deaths	0	0
Number of serious AEs other than death	0	0
Number of other significant AEs	0	0
Number (%) of subjects with discontinuations due to AEs	0	1 (5%)
Total number of AEs	19	28
Severity of AEs		
- Mild	19	25
- Moderate	0	3
- Severe	0	0
- Not assessed	0	0
Number (%) subjects with AEs	11 (61%)	10 (53%)
Maximum number of AEs per patient	4	6

Table S2 Number (%) of subjects with the most commonly reported adverse events, summarised over all treatment groups

Preferred term [a]	**AZD8309 300 mg** **n=18**	**Placebo** **n=18**
Pyrexia	5 (28%)	3 (17%)
Headache	2 (11%)	4 (22%)
Dizziness	0	3 (17%)
Nasal congestion	2 (11%)	3 (17%)
Diarrhoea	3 (17%)	1 (6%)
Rhinitis	0	2 (11%)
Pharyngolaryngeal pain	0	2 (11%)

[a] Only AEs that occurred in 2 or more subjects

There appeared to be no changes in any mean laboratory values over time, with the exception of leucocytes and neutrophils where decreases of approximately $1x10^9$/L during the AZD8309

treatment period were seen for both measures. Both parameters had returned to baseline values by the follow-up visit.

FEV_1 changes seen within the first hour post-LPS challenge were very similar for placebo and AZD8309 300 mg; however the speed and extent of recovery of lung function in the AZD8309 group was greater than that seen with placebo ($p<0.05$). The mean FEV_1 after treatment with AZD8309 was 4.28 and after placebo was 4.23, a numerically very small difference.

An increase in body temperature was seen from a mean of 35.9°C pre-dose to 36.9°C at 8 h post-LPS challenge. This had dropped back to 36.3°C at 24 h post-LPS challenge. There were no differences between AZD8309 and placebo in these findings.

There were no differences between the treatment groups in pulse rate, systolic or diastolic blood pressure, and no findings of clinical concern in 12-lead ECG.

Conclusions

- [redacted]

Date of the report

15 November 2006.